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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,145	SEIBERT, KAREN	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/23/04; 5/12/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This application claims priority under 35 U.S.C § 119(e) from the provisional application 60/458595, filed 28 March 2003. Claims 1-15 are currently pending and are considered on the merits herein.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15 are provisionally rejected on the ground of nonstatutory double patenting over claims 2-15 of copending Application

No. 10/772,760. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '760 application claims a method of treatment for otic –disorder related complications by the use of a combination of Cox-2 inhibitors and otic agents including glucocorticoids, in particular hydrocortisone, prednisone, fluprednisolone, dexamethasone, betamethasone, cortisone and prednisolone. Cox-2 inhibitors of the claimed invention include celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib and a list of chromene Cox-2 inhibitors.

The claims of the instant application is drawn to a method of providing a steroid-sparing benefit to a subject that is in need of, or that is presently receiving, a corticosteroid, the method comprising administering to the subject a Cox-2 inhibitor in combination with a corticosteroid. Cox-2 inhibitors of the claimed invention include celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, a list of chromene Cox-2 inhibitors, and gluccorticoids include hydrocortisone, prednisone, fluprednisolone, dexamethasone, betamethasone, cortisone and prednisolone.

Thus, the instant claims 1-15 are deemed to be anticipated by claims 2-15 of the copending application No. 10/772,760.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the preparation of a combination of celecoxib and prednisone in the particular dosage form given in example 2, does not reasonably provide enablement for diseases and disorders, such as inflammation, pulmonary hypertension, asthma, retinopathy, diabetic retinopathy, edema formation, arthritis, rheumatoid arthritis, multiple sclerosis, Crohn's disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock, septic shock, ulcerative colitis, reperfusion injury of the myocardium and brain, osteoarthritis, psoriasis vulgaris, lichen planus, keloids, urticaria pigmentosa, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease,

diabetes insipidus, rhinitis, allergic conjunctivitis, vernal conjunctivitis arterial restenosis, artherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, lupus, autoimmune diseases, transplant rejection and graft versus host disease or septic shock, inflammation and cytokine-mediated chronic tissue degeration, cancer, cachexia, conjunctivitis, dermatitis, muscle wasting, depression, inflammatory bowel disease, allergic responses to insect and arthropod bites, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimers disease, spinal cord trauma, head injury, joint injury, multiple sclerosis, tumor growth and cancerous invasion of normal tissues.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of corticosteroid responsive diseases and disorders.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on treating a large category of pathological conditions, listed above.

The state of the prior art: The prior art includes extensive disclosures of the use of a wide variety of compounds with Cyclooxygenase-2 inhibitory activity. "Corticosteroids" are defined to encompass "glucocorticoids.' (Sepcification, Page 6, lines 21-27). The prior art in the area of glucocorticoids include a wide variety of compounds with activity in a multiple biological process.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would

recognize that the recitation encompasses many pathological conditions, which are known to be involved various, many possible, and different, separate and independent pathology, etiologies, or symptoms. For example, in case of artherosclerosis, the pathology involved is that atherosclerotic plaque consists of accumulated intracellular and extracellular lipids, smooth muscle cells, connective tissue (see the Merck Manual of Diagnosis and Therapy (17th ED) (1999), page 1654-1657, PTO-892), whereas the particular inflammatory bowel condition, Crohn's disease, is known to be involved in mucosal lesion, crytitis, and crypt abscesses (see the Merck Manual of Diagnosis and Therapy (17th ED) (1999), page 302-303, PTO-892).

The skilled artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic regimen. No single chemotherapeutic drug is useful for the treatment of every case of cancer. Indeed, some types of cancer to not respond well to any known chemotherapeutic drugs. According to the Merck Manual of Diagnosis and Therapy (Reference included with PTO-892), Hepatocellular carcinomas and renal cell carcinomas are not generally improved by chemotherapy. Acute lymphoblastic leukemia, on the other hand, responds well to a number of drugs, including vincristine, anthracyclines, and aspariginases, while acute mylogenous leukemia, on the other hand, responds to fewer drugs and is usually treated with cytarabine in combination with daunorubicin or idarubicin.

Thus, the skilled artisan would view that the treatment of different types of cancer and Crohn's disease by administering the same particular combination herein, is highly *unpredictable*. Therefore, the skilled artisan would view that the treatment of all conditions/diseases herein, more than 60 conditions/diseases listed in claim 11 herein by administering the same particular combination of compounds herein, is highly *unpredictable*.

Thus, the skilled artisan would view that the treatment of all inflammatory conditions, all tumor growth and cancerous invasion of cells, all pain or all cough and rhinitis conditions by administering the same combination herein, is **highly unpredictable**.

In regard to these *Wands* factors, (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary:

Moreover, it is noted that the specification merely provides a prophetic example of a combination of a corticosteroid with a Cox-2 inhibitor. There are no examples of the administration of said combination to any patients. There are no examples of the administration of said combination to patients with any of the specific diseases listed in claim 11.

Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad treatment of any pathological conditions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search and undue experimentation for the

embodiments of treating any pathological conditions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation*, with no assurance of success.

Claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case Claim 1 recites a combination of a corticosteroid and a Cox-2 inhibitor.

Claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recited chromeneinhibitors in claim 7, does not reasonably provide enablement for all compounds that might have activity against Cyclooxygenase-2. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case Claim 1 recites a combination of any corticosteroid with any Cox-2 inhibitor. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 where the Court set fourth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex Parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the invention: The claimed invention is a therapeutic method for "providing steroid-sparing benefit to a subject that is in need of, or that is presently receiving, a corticosteroid" by the use of a combination of a Cox-2 inhibitor and a corticosteroid.

The state of the prior art: The prior art includes extensive disclosures of the use of a wide variety of compounds with Cyclooxygenase-2 inhibitory activity. "Corticosteroids" are defined to encompass "glucocorticoids.'

(Sepcification, Page 6, lines 21-27). The prior art in the area of glucocorticoids include a wide variety of compounds with activity in a multiple biological process.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art:

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with

drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. **Thus, the teachings of the book clearly support that the instant claimed invention, administering a** combination of any Cox-2 inhibitor and any corticosteroid to a host (e.g., a human) **is highly unpredictable.**

The level of predictability in the art

As seen by Goodman & Gilman, the art of combination therapy is unpredictable. Drug-drug interactions are known to be beneficial or adverse, yet there is no way to know until the drugs are actually tested in combination with each other.

The Breadth of the claims: Claim 1 includes any molecule with any level of Cyclooxygenase-2 inhibitory activity. Aspirin is known to have inhibitory

activity against the class of cyclooxygenase enzymes, including Cyclooxygenase 2. Corticosteroids also are known to have activity against cyclooxygenase enzymes. For example, Dexamethasone, a widely used corticosteroid, is well known to inhibit Cyclooxygenase-2 expression. (Lee et. al. Page 25934, Abstract; PTO-892, Included by the applicant). Claim 1's recitation of corticosteroid's encompasses any molecule with glucocorticoid activity. There is a large class of molecule with varying levels of glucoccorticoid activity. The claim will read on any molecule with any level of glucocorticoid activity when used in combination with any molecule with any level of Cyclooxygenase activity.

The amount of direction or guidance presented:

Table 3 of the specification gives a listing of the dosage levels of several known corticosteroids. (Specification, Page 133). The dosage levels of Cox-2 inhibitors is described in general as 0.01-140mg/kg. (Specification, Page 157, Paragraph 266, lines 13-18).

The presence or absence of working examples:

The only example that describes a combination of corticosteroid and a cox-2 inhibitor, the prophetic example, Example 2, describes the combination of celecoxib and prednisone. The dosage levels were 10mg prednisone and 200mg celecoxib. The example does not give any guidance as to which disease is this particular composition is used to treat or prevent.

The quantity of experimentation necessary: In order to achieve "steroid-sparing benefit," for every corticosteroid in combination with every compound with Cox-2 inhibitory activity, a great deal of experimentation is necessary. In order to lower the corticosteroid dosage in combination therapy in comparison to stand-alone corticosteroid treatment, the effective dosage level a corticosteroid in combination with a Cox-2 inhibitor need to be determined.

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples in all ranges, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of conditions claimed herein absent undue experimentation.

Claims 10-12 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the administration of a combination of corticosteroid and a Cox-2 inhibitor, does not reasonably provide enablement for **prevention** of a broad range of diseases as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The Nature of the invention: The claimed invention is a therapeutic method for preventing or treating a corticosteroid-responsive disease or disorder by the use of a combination of a Cox-2 inhibitor and a corticosteroid.

The state of the prior art: The prior art includes extensive disclosures of the use of a wide variety of compounds with Cyclooxygenase-2 inhibitory activity. "Corticosteroids" are defined to encompass "glucocorticoids.' (Sepcification, Page 6, lines 21-27). The prior art in the area of glucocorticoids include a wide variety of compounds with activity in a multiple biological process.

The relative skill of those in the art: The relative skill of those in the art is high, with a typical practitioner having obtained a PhD or equivalent advanced degree.

The predictability or unpredictability of the art: Prevention of any corticoid responsive disease is not the same as the treatment of said symptoms. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms?

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose

necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many of the therapies that are useful for treating a disease are not useful preventing the disease. For example, antibiotics, chemotherapeutics and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims:

Claim 10 is directed to any disease in which a corticosteroid will have any effect, and the treatment involves the administration of a combination of that contains any amount of a corticosteroid and any amount of a Cox-2 inhibitor.

Claim 11 is directed to the use of said combination for a list of diseases and disorders that include inflammation, rheumatoid arthritis, multiple sclerosis, benign and malignant proliferative skin diseases, rhinitis (common cold), pain and cough. As such, the claims are very broad.

The amount of direction or guidance presented: There is no clear guidance given for the prevention of any diseases by the use of the combination of a corticosteroid and Cox-2 inhibitor.

The presence or absence of working examples: There are no working examples for the prevention of any diseases.

The quantity of experimentation necessary:

The usefulness of the combination of the two types of pharmaceuticals, corticosteroid and Cox-2 inhibitors, to treat corticosteroid-associated diseases is no guarantee that it will be effective in preventing any said diseases from occurring in the long term. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy.

In particular, one skilled in the art would need to know whether the regular administration of the combination in the claimed form over the long term would adversely affect the health of the subject. Additionally, one skilled in the art, in order to practice the invention for prevention of disease would need to know whether the preventive effect remains potent over the long term. Unless the therapy absolutely eliminates all of the corticosteroid-responsive diseases over the long term, the drug cannot be considered a preventive therapy.

Furthermore, it is not clear corticosteroid-responsive diseases will be prevented by the use of the combination of a Corticosteroid and a Cox-2 inhibitor.

In order to answer these questions, in the absence of any existing data, one skilled in the art, in order to practice the invention, would have to undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or sheeps. Accomplishing such a task for the myriad of symptoms that can be considered menopausal complaints would require an undue amount of experimentation for the practice of full range of the claimed invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the breadth of the claims, the unpredictability of the art, and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of diseases claimed herein absent undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "steroid-sparing benefit" recited in claim 1 renders the claims indefinite as to the benefit received by the use of the method. The specification describes;

> "Therefore, oral corticosteroid therapy requires careful monitoring by the prescribing physician, and continual efforts to wean the subject from the corticosteroids as soon as possible. Because many of the side effects from corticosteroid usage appear to be dose-dependent, clinicians have continued to search for alternative therapies that reduce the level of corticosteroids required for a particular benefit level (hereinafter referred to as steroid-sparing benefits)"

It is not clear which of the benefits and the benefit level that is encompassed by the claims.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "a subject that is in need of" in claim 1 renders the claim indefinite. The expression does not show which diseases, disorders or symptoms are treated by the use of the combination.

Claims 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "corticosteroid-responsive disease or disorder" renders the claims indefinite as the disorder or disease encompassed by the claims. It is not clear what disorders or diseases would be considered "corticosteroid-responsive."

Claims 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "inflammation-related disorder" renders the claims indefinite as the disorder or disease encompassed by the claims. It is not clear what disorders or diseases would be considered "inflammation related disorder."

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The expression "Cox-2 inhibitor in combination with corticosteroids" renders the claim indefinite. Corticosteroids are well known to have Cox-2 inhibitory activity themselves without the further addition of another Cox-2 inhibitor. (Rocca et. al. Page 605, Column 2, Paragraph 2, lines 1-5; PTO-892, Cited by the examiner).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 8-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz et.al, (PTO-892, Cited by the examiner).

Schwartz et. al, teaches the use of a combination of Rofecoxib, a Cox-2 inhibitor in combination with prednisolone for the treatment of inflammatory disorders, rheumatoid arthritis and osteoarthritis. (Page 187, Abstract and Column 1, First Paragraph). Note that Rofecoxib is a selective Cox-2 inhibitor. The drugs were administered at the same time. (Page 188, Column 2, lines 8-13). Both prednisone (Deltasone) and Rofecoxib were used in their pharmaceutical form. (Page 188 Column 1 Paragraph 5 and Column 2, Paragraph 1).

Claims 1-2, and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et. al. (PTO-892; Cited by the examiner).

Kim et. al. teaches the use of aspirin in combination with prednisone. (Page S12, Column 2, Meeting Abstract). Kim et. al. teaches the use of 80mg aspirin with 15mg of prednisone. Note that aspirin is a non-selective inhibitor of cyclooxygenase, and inhibits both of its isoforms, Cox-1 and Cox-2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-7 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et. al (PTO-892, Cited by the examiner), in view of Carter et.al. (U.S. Patent No. 6,034,256, PTO-892; Cited by the examiner)

Schwartz et. al teaches the use of a Cox-2 inhibitor in combination with a corticosteroid for the treatment of inflammation. (Page 187, paragraph 1). Schwartz et. al further teaches the use of a Cox-2 inhibitor and a corticosteroid at the same time. (Page 188, Column 2, lines 8-13). Schartz et. al teaches that patients receiving nonsteroidal anti-inflammatory drug therapy may also require administration of

corticosteroids, particulary for patients with rheumatoid arthritis. (Page 187, Abstract, lines 1-5). Schwartz et.al further notes that Cox-2 inhibitors are a class of nonsteroidal anti-inflammatory drugs. (Page 187, Paragraph 1, lines 4-15).

Schwartz et. al does not expressly teach the use of celecoxib or the use one of the chromene compounds in claim 7. Schwartz et. al. does not expressly teach the use of a kit comprising the two type of compounds.

Carter et. al. describes the use of 6-chloro-7-(1,1dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid as a Cox-2 inhibitor for treating inflammation. (See Abstract, Column 18, lines 29-30). Note that said compound is a chromene compound described in claim 7.

It would have been obvious to a person of ordinary skill in the art at the time invention was made to use a chromene compound, in particular 6-chloro-7-(1,1dimethylehtyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid in combination with a corticosteroid for the treatment of inflammation. Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine two particular drugs in a kit.

One of ordinary skill in the art would have been motivated to do this because Schartz et. al teaches that patients receiving nonsteroidal anti-inflammatory drug therapy may also require administration of corticosteroids, particulary for patients with rheumatoid arthritis, and chromenes, in particular 6-chloro-7-(1,1dimethylehtyl)-2-trifluoromethyl-

2H-1-benzopyran-3-carboxylic acid, is well known for its activity as a nonsteroidal anti-inflammatory drug, and also known as a Cox-2 inhibitor.

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sekut et. al (U.S. Patent No. 6,054,487; PTO-892, Cited by the examiner), in view of Carter et.al. (U.S. Patent No. 6,034,256, PTO-892; Cited by the examiner) and further in view of Marnett et. al. (PTO-892, Cited by the examiner)

Sekut et. al discloses a method for modulating responsiveness to corticosteroids by the combination with interferon antagonists. (Column 2, lines 5-10). It further discloses the combination of corticosteroids with inhibitors of IFN-γ production to achieve a "steroid sparing effect." (Abstract and Column 20, Paragraph 3, lines 54-60). Sekut et. al points out that "While therapeutically beneficial, the use of corticosteroids is associated with a number of side effects, ranging from mild to possibly life threatening." Sekut further notes that, "Accordingly, methods and compositions that enable the use of a lower effective dosage of corticosteroids (referred to as the "steroid sparing effct") would be highly desirable to avoid unwanted side effects. (Column 1, Paragraph 2, lines 23-28 and 38-43). Sekut et. al discloses the use of corticosteroids for the treatment of immune and inflammatory disorders. (Column 1, lines 1-5).

Sekut et. al. does not expressly disclose the use of corticosteroids in combination with Cox-2 inhibitors or their use together as a kit.

Carter et. al discloses a class of benzopyran compounds, in particular 6-chloro-7-(1,1dimethylehtyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (one of the chromene compounds listed in claim 7) as Cox-2 inhibitors. (Abstract and Column 18, lines 28-32). Carter et. al further their use as anti-inflammatory agents. (Claim 8, Column 18, lines 32-63).

Marnett et. al discloses the use of several Cox-2 inhibitors as anti-inflammatory agents. (Page 465, Abstract, lines 5-10, and Figure 2). Marnett et. al discloses the use of Celebrex (also known as celcoxib) as an anti-inflammatory agent. (Page 466, Column 1, lines 6-8, and Figure 2).

It would have been obvious to a person of ordinary skill in the art at the time invention was made to use a Cox-2 inhibitor, in particular celecoxib or 6-chloro-7-(1,1dimethylehtyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, in combination with a corticosteroid for the treatment of inflammation, to optimize the effective amounts of active agents in the composition to be administered. Furthermore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine two particular drugs in a kit.

Therefore one of ordinary skill in the art would have reasonably expected that combining a glucocorticoid with a Cox-2 inhibitor, both

known useful for treating inflammation, would improve the therapeutic effects for treating the same disease, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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6/24/06

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